Current Status of Drug Development and Clinical Trials Update -

Every Single One Tour - Los Angeles

January 21, 2017

Stanley Nelson, MD
Professor
Human Genetics
Center for Duchenne Muscular Dystrophy at UCLA
Review Committee Member: Parent Project Muscular Dystrophy CDCC program
Where were we?

- LATE 1990’s
  - *Total NIH funding for MD is $17M*
  - No new drugs in development
  - Average lifespan for DMD is late teens
  - No guidelines for care
  - No patient registries
  - Minority of patients on steroids
Muscular dystrophy related deaths in US from CDC: 1985-2005

Kenneson et al, 2010
Most early mortality from muscular dystrophy due to DBMD

**80% of muscular dystrophy deaths from DBMD under age 30!**

Data from Kenneson, et al 2010
Improvements in care have reduced mortality of DBMD over past 20 years (US)

Data from Kenneson, et al 2010
Schematic Natural History of DMD

Prior to Treatment, 1960s
- 5 Years: Loss of Standing, Loss of Ambulation, Loss of Self-Feeding
- 9 Years: 
- 14 Years: 
- 20 Years: Death

- 5 Years: Loss of Standing, Loss of Ambulation, Loss of Self-Feeding
- 9 Years: Ventilation
- 14 Years: Death

Contemporary: With Steroids and Improved Cardiac Management
- 5 Years: Loss of Standing, Loss of Ambulation, Loss of Self-Feeding
- 9 Years: 
- 14 Years: 
- 20 Years: Death

Steroids affect disease progression in DMD over the entire course of the disease, prolonging clinically meaningful functions (time to loss of milestones)
Where Are We Now?

- Total NIH funding for MD is $17M
- No new drugs in development
- Average lifespan for DMD is late teens
- No guidelines for care
- No patient registries

• TOTAL NIH funding all MDs ($78M)
• (UCLA alone has about $4 million in new MD funding this past year)
• 30 different drugs tested in trials in DMD
• 19 new drugs developed for DMD in trials
• 4 repurposing trials testing in DMD
• >12 drugs in preclinical development
• Care guidelines for DMD disseminated globally & update underway
• DMD Lifespan increasing if care guidelines followed
• Natural History Studies, Registries and other drug development tools
• First FDA approval for Duchenne: Exondys 51
Center for Duchenne Muscular Dystrophy at UCLA

CENTER FOR DUCHENNE MUSCULAR DYSTROPHY

Directors:
M. Carrie Miceli, Ph.D.
Stanley Nelson, M.D.
Melissa Spencer, Ph.D.

Executive Committee
Core Directors
Linda Baum
Rachelle Crosbie-Watson
Ronald Victor

External Advisors
Kathryn Wagner, Kennedy Kreiger
Jeffrey Chamberlain - Univ. Wash
Glenn Walter - Univ. Florida

ENRICHMENT PROGRAMS

Seminar series
Focused Working Groups
Muscle Cell Biology Training Program (undergraduate + graduate education)

Pilot and Feasibility Seed Grant Program
Annual Retreat

ParentProjectMD.org
Clinical

- **Care**
  - Multidisciplinary Care Team
  - CCS Special Care Clinic
  - MDA Clinic
  - PPMD Certified Duchenne Care Center.

- **Trials and Human Subjects Research**
  - >20 clinical trials/human subjects studies have been initiated at the CDMD.
  - Clinical Assessment Team enables rapid participation in pharma sponsored trials.
  - two UCLA developed compounds in development
FUNCTIONAL ASSESSMENT LAB
EILEEN FOWLER, PT, PHD

Christy Skura, PT-dedicated PT for trials

Marcia Greenberg, MS. PT    Lauretta Staudt, MS, PT    Kent Heberer, MS. PhD
• Muscle Cell Biology Training Program
  *Track within Cell & Developmental Biology Home Area*

• **Training Activities**
  – Retreat, Poster Sessions, Journal Club, Working Groups

• **New T32 Training Grant**
  – PI Crosbie-Watson, Co-I M. Carrie Miceli.

• **PS121: Innovative course on DMD: teaching depth and critical thinking skills**
  – *Team taught by over 10 faculty + CTSI*
  – *New online course for all UC students*
  – *PPMD funding allows broader availability soon!*

Rachelle Crosbie-Watson, Ph.D.
CDMD Education Liaison
UCLA PS121
DISEASE MECHANISMS AND THERAPIES

Duchenne Muscular Dystrophy

- Online upper division elective
- 5 units
- Live online discussions
- All readings available free online
- Ideal for careers in health care, medicine, and research
- Chancellor’s Distinguished Teaching Award

For information contact Dr. Rachelle Crosbie-Watson at: rcrosbie@physci.ucla.edu

UCLA Enrollment: my.ucla.edu
UC Wide Enrollment: crossenroll.universityofcalifornia.edu
“Modulating Calcium Signals to Boost AON Exon Skipping for DMD” MICELI
“Evaluation of engraftment potential of novel skeletal myogenic progenitors derived from hiPSCs” PYLE
“Therapeutic development of osteopontin inhibitors for Duchenne” SPENCER
“Validating Cardiac MRI Biomarkers and Genotype-Phenotype Correlations for DMD” ENNIS
“Mechanisms controlling skeletal muscle mitochondrial function and metabolic health.”
“Pharmacogenomics of Statin Therapy” REUE
“Stem Cell Approaches for Combination DMD Exon Skipping Therapy” MICELI/PYLE/SPENCER/Nelson
“CRISPR-cas9 repair of stem cells Pyle/Spencer
NIH Wellstone Muscular Dystrophy Center U54 AR052646-07 (PI: Sweeney-UPenn, CoI’s: Nelson, Spencer, Miceli, Crosbie-Watson)
“Failed Regeneration in the Muscular Dystrophies: Inflammation, Fibrosis and Fat”
Validating Cardiac MRI Biomarkers and Genotype-Phenotype Correlations for DMD

- **SA-1 Validation**
- **SA-2 Sensitivity**
- **SA-3 Genetics**

**Year-0**
IRBs, MRAs, C2Ps, Licensing, Advertise, Recruit, Technical Refinements, Database, etc.

**April 1, 2016**

**Year-1**

- **Technical Refinements**
- **12+6 Healthy**
- **18+18 DMD**

**Year-2**

- **Analyze & Report Results**

**Year-3**

- **30 DMD 6mo f/u**
- **30 DMD 6mo f/u**
- **40 DMD from USA**

**Year-4**

Accuracy, Precision, Repeatability Intra- & Inter-observer Intra- & Inter-institute

Cardiac MRI Biomarker Changes on 6 month follow-up.

Genotype-Phenotype Correlations

Contact: Dr. Daniel Ennis, Ph.D. (ennis@ucla.edu)
Brain Imaging in Duchenne Muscular Dystrophy

Goals

- Probe Brain Imaging Biomarkers
- Study Brain Network Connectivity Disruptions
- Associate imaging biomarkers with neuropsychological and cognitive function

Preliminary Data

cortical thickness  cerebral perfusion
Ongoing Study — Recruiting participants

UCLA Research Study for Males 7 yrs or older with Duchenne Muscular Dystrophy

Eligibility

- Male with Duchenne Muscular Dystrophy, age 9 - 15 years old
- No medical implants or other metal (fillings are OK) in the body
- No diagnosis of injury to the brain or spinal cord

Involvement

- A single MRI brain scan. MRI is very safe and does not use radiation
- Cognitive and Behavioural assessments

Compensation for Time (up to $120)

- $50 for the brain scan + $12 for parking
- $65 for participating in the cognitive assessments

For more information please contact

Ronald Ly: rqly@mednet.ucla.edu / 310-206-9012
Shantanu Joshi: sjoshi@mednet.ucla.edu / 310-439-9490
Duchenne Genetic Modifier Project

Search for rare gene differences in mild vs. severe DMD

Cell Resource Core (Miceli)
Evaluation of mutation effect: Miceli, Crosbie-Watson,
Outreach

Ms. Amy Martin, CDMD Community Liaison works with local families to improve information dissemination about state of the art research and clinical care in Duchenne.

- Annual CDMD retreat
- Information sessions (e.g., mobile arm supports, PT, etc).
- FACES Meetings
- Clinical Trial Roundtable
- Annual Event Duchenne Gala
Duchenne Therapeutic Approaches

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough

- Dystrophin Restoration /Replacement

- Steroid Replacement
- Anti-Fibrotics
- Inflammation & Fibrosis
- Calcium Regulation
- Ryanodine Receptors
- Calcium Homeostasis

- Muscle Growth and Protection

- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophin Upregulation

- Stem Cells

- Traditional Cardiac Drugs

- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- Cardiac
- Blood Flow
- Mitochondria

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE
Study Types

• Multi-Phase Clinical Trials
  – Pre-clinical: lab and animal studies
  – Phase I: First in humans (mechanistic, usually in healthy volunteers, dosing, small n); assess safety
  – Phase IIa: Assess dose requirements
  – Phase IIb: Assess efficacy; “Pivotal” (can combine a and b, testing both efficacy and toxicity); larger than phase I
  – Phase III: Classical RCT; 1000-3000 subjects
  – Phase IV: Post-Marketing; monitor long term effects

• Clinical observation, Natural History Studies

• Basic science specimen studies
What is a Clinical Trial?

• A trial is an experiment, not a therapy
• Potential benefits come with Risks are not fully KNOWN
• Trial may be stopped early due to:
  – Too much toxicity that was unexpected
• Important to pay attention to the informed consent
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**PPMD Engagement in Clinical Trials**

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- **Target/MOA**
- **Study Design**
- **Some inclusion/exclusion criteria**
- **Endpoints**
- **Sites**

*Pipeline graphic represents the clinical trial FAQ sheets included in this booklet and it not intended to be a comprehensive list.*
Duchenne Therapeutic Approaches

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough

- Steroid Replacement
- Anti-Fibrotics
- Inflammation & Fibrosis
- Calcium Regulation

- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators

- Dystrophin Restoration /Replacement
- Stem Cells
- Traditional Cardiac Drugs
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- Cardiac
- Blood Flow
- Mitochondria
- Stem Cells

- Treating Duchenne
- Muscle Growth and Protection

- Ryanodine Receptors
- Calcium Homeostasis

- Relevant Therapies:
  - RycalARM210
  - Carmeseal-MD™
  - AT-300
  - Wave Life Sciences Medications
  - Translarna™ (ataluren)
  - RTC13
  - NS-065/NCNP-01 for Exon 53 Skipping
  - Gene Transfer of Micro-Dystrophin
  - Exon 2 duplication strategy
  - BMB-D001
  - AAV Microdystrophin Gene Therapy
  - Spironolactone and Eplerenone
  - CAP-1002
  - BMS-986089
  - Ezutromid (SMT C1100)
  - Biglycan
  - MTB-1
  - Epicatechin
  - Vamorlone (VBP15)
  - NBD Peptide
  - Givinostat (ITF2357)
  - FG-3019
  - CAT-1004

- Other Therapies:
  - Laminin-111
  - iPS Cell therapy
  - Follistatin Gene Transfer
  - Ezutromid (SMT C1100)
  - Biglycan
  - MTB-1
  - Epicatechin
  - Vamorlone (VBP15)
  - NBD Peptide
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  - CAT-1004
MoveDMD®: Clinical Trial of Edasalonexent (CAT-1004) in Boys with Duchenne Muscular Dystrophy
Edasalonexent Inhibits NF-κB and Shows Disease-Modifying Effects in DMD Models

**Pre-clinical studies**

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<th>Reduced inflammation and fibrosis</th>
<th>Enhanced muscle regeneration</th>
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**Diagram**

- **ABSENCE OF DYSTROPHIN** + **MECHANICAL STRESS**
  - Activated NF-κB (protein)
  - MRI of muscle
  - Reduced muscle degeneration
  - Reduced inflammation and fibrosis
  - Enhanced muscle regeneration
  - Satellite stem cell
  - Myoblasts
### MoveDMD Phase 2 Trial with 36-week Open-Label Extension Underway

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<th>12-week, randomized, double-blind placebo-controlled trial</th>
<th>36-week open-label extension, all patients receiving edasalonexant</th>
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N ~ 10 per arm  
- Edasalonexent 67 mg/kg per day  →  Edasalonexent 67 mg/kg per day  
- Edasalonexent 100 mg/kg per day  →  Edasalonexent 100 mg/kg per day  
- Placebo  →  Edasalonexent 67 mg/kg or 100 mg/kg per day

**Study Population:** All mutations, ages 4 – 7, steroid naïve or off steroids for ≥6 months

- **Part A Results (treatment for 1 week)**
  - No safety signals and generally well tolerated
  - Edasalonexent plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed
  - Positive NF-κB biomarker data
- **Safety:**
  - Monitored by investigators, Sponsor and Data Safety and Monitoring Committee
- **Sites:**
  - University of Florida; Shriners, Portland OR; CHOP, Philadelphia PA; Nemours Children’s Hospital, Orlando FL; UCLA, CA
### MoveDMD Phase 2 Trial with 36-week Open-Label Extension Underway

**12-week, randomized, double-blind placebo-controlled trial**

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- N ~ 10 per arm

**36-week open-label extension, all patients receiving edasalonexent**

- Edasalonexent 67 mg/kg per day
- Edasalonexent 100 mg/kg per day
- Edasalonexent 67 mg/kg or 100 mg/kg per day

**Study Population:** All mutations, ages 4 – 7, steroid naïve or off steroids for ≥6 months

**Next Year**

**Non-Ambulant Boys**

**Additional Trial in 4-7 Year Olds**

- Part A Results (treatment for 1 week)
  - No safety signals and generally well tolerated
  - Edasalonexent plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed
  - Positive NF-κB biomarker data

- Safety:
  - Monitored by investigators, Sponsor and Data Safety and Monitoring Committee

- Sites:
  - University of Florida; Shriners, Portland OR; CHOP, Philadelphia PA; Nemours Children’s Hospital, Orlando FL; UCLA, CA
• **Primary Endpoint:**
  – Changes in MRI of muscles, No safety signals and generally well tolerated

• **Secondary Endpoints:**
  – 10 meter walk/run, 4-stair climb, time to stand

• **Additional Assessments:**
  – Muscle strength, North Star ambulatory assessment
  – PODCI questionnaire (pediatric outcome data collection instrument)

• **Frequency of Visits**
  – Monthly at first, then will decrease over time
Vamorolone
A potential steroid alternative for Duchenne
A Phase 2a Open Label Multiple Ascending Dose Study to Assess the Safety, Tolerability, PK/PD

- **Sponsor:** ReveraGenBioPharma, Inc.
- **Purpose:**
  - To determine whether a new medication is safe and well tolerated for boys with DMD
- **Age:**
  - (DMD) ages $\geq 4$ and $< 7$ years old
- **30 boys, never taken steroids**
- **Length:** 4 weeks
- **Extension study for 24 weeks or longer**
Study Design

4 weeks n = 30
- Vamorolone 1 mg/kg/day
- Vamorolone 2 mg/kg/day
- Vamorolone 4 mg/kg/day
- Vamorolone 8 mg/kg/day

Extension Study 24 weeks or longer

Approx. 6 visits over 1-2 months

Approx. 9 visits over 6 months
Endpoints

• Primary:
  – Number of participants with treatment-related adverse events

• Secondary:
  – Peak Plasma concentration (day 1, week 2)
  – Serum Biomarkers

• Other measures (4 weeks)
  – Quantitative Muscle Testing (QMT)
  – Time to Stand Test (TTSTAND)
  – Time to Climb Test (TTCLIMB)
  – Time to Run/Walk 10 Meters (TTRW)
  – North Star Ambulatory Assessment (NSAA)
  – 6 Minute Walk Test (6MWT)
8 Sites

- Lurie Children’s Hospital of Chicago
- CNMC, Washington DC
- Duke Children’s Health Center, Durham NC
- UT Southwestern, Dallas
- U of Pittsburgh
- UCDavis, Sacramento
- University of Florida, Gainesville
- Nemours Children’s Health System, Orlando
FG – 301 An Investigational Therapeutic Monoclonal Antibody to Inhibit the Activity of Connective Tissue Growth Factor (CTGF)
What is CTGF?

- CTGF is part of fibrotic process, correlates to fibrosis
- In animal, overexpression causes severe fibrosis
- Excess CTGF interrupts normal myoblast differentiation, causing excess myofibroblasts, abnormal cells, collagen, fibrosis
In DMD, repeated cycles of muscle degeneration and regeneration lead to replacement of dystrophic muscle by fibrotic tissue and fat.

Slowing or reversal of fibrosis is expected to slow or reverse loss of muscle function.
Trial of FG-3019-079

- Phase 2 open Label, single arm study of up to 22 non-ambulatory boys (wheel chair dependent for <5 years)
- Purpose: Estimate efficacy, evaluate safety, assess PK
- Age:
  - 12 years and older
- **Stable steroid regimen for at least 6 mos.**
- Dosing: IV infusion every 2 weeks for up to 2 years
Some Inclusion Criteria

- Brooke Score for Arms and Shoulders ≤5 (can’t raise hands to mouth but can pick up a pen or coins from table)
- Able to perform spirometry: FVC ≥ 50% predicted
- Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC
- Able to undergo cardiac and extremity (upper arm) MRI
- Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 mos. prior to day 0
- Stable regimen of heart failure cardiac medications
Efficacy Endpoints

• Change in pulmonary function:
  – Forced vital capacity
  – Maximum inspiratory flow, Maximum expiratory flow
  – Peak expiratory flow
  – Peak cough flow

• Change in upper body muscle function:
  – PUL, grip strength, pinch strength, Brooke score

• Change in muscle fibrosis and/or fat by MRI of biceps and heart

• Changes in QOL
SITES

• Washington University, St Louis, MO
• Cincinnati Children’s, Cincinnati, OH
• UCSF Benioff Children’s Hospital, San Francisco, CA
• UPMC, Pittsburgh, PA
• Children’s Hospital, Aurora, CO
• University of Iowa, Iowa City, IA
• UCLA, Los Angeles, CA
Mitochondria

Mitochondria

Many targets for therapeutic intervention in Duchenne—with the idea that we will ultimately treat Duchenne using a

Research is at the heart of advances in treatment and care for Duchenne. The chart below gives an overview of the

DUCHENNE THERAPIES

providing data that is crucial in the fight to end Duchenne.

Remember to register on DuchenneConnect to stay up-to-

date on ALL therapies that are currently in development.

EXAMPLES INCLUDE:

- RycalARM210
- AT-300
- Wave Life Sciences Medications
- Exon 2 duplication strategy
- BMB-D001
- AAV Microdystrophin Gene Therapy
- CAP-1002
- Stem Cells
- Ryanodine Receptors
- Calcium Homeostasis
- Exon-Skipping
- Stop-Codon Readthrough
- Steroid Replacements
- Anti-fibrotics
- Utrophin Upregulation
- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophin Upregulation
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers
- Stem Cells
- Cardiac Drugs
- Traditional Cardiac Drugs
- Calcium Regulation
- Calcium Homeostasis
- Inflammation & Fibrosis
- Mitochondria
- Blood Flow
- Cardiac
- Dystrophin Restoration
- Dystrophin Restoration/Replacement
- CRISPR/Cas9
- Stop-Codon Readthrough

Muscle Growth and Protection

Treating Duchenne

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE
Givinostat
A Histone Deacetylase (HDAC) Inhibitor for the Treatment of Duchenne
Italfarmaco - Givinostat

• Histone deacetylase inhibitor (HDAC)
  – HDAC (an enzyme involved in transcription and post translational modifications) is upregulated in dystrophic muscle
  – Inhibiting HDAC promotes transcription of pro-muscle regeneration factors, i.e. follastatin
  – In mdx mouse, HDAC inhibition
    • Increases size of myofibers
    • Decreases inflammation
    • Prevents formation of fibrosis
Givinostat Status

• Positive Phase 2 results from Italy
• N = 20, 3 doses
• Age: 7-<11 treated for < 24 months
• After 12 months:
  – Decreased activity of HDAC
  – Increased muscle fiber size
  – Decreased fibrosis, fatty replacement, necrosis and the mean # of hyper-contracted fibers
  – Increased regenerative fibers with no depletion of pool of satellite cells
• Next, Phase 3
Givinostat Trial Phase 3 (in planning stage)

- Randomized, double blind, placebo controlled, multi-center
- 2:1 randomization
  - 142 in treatment arm
  - 71 in placebo arm
- 19 months duration
  - Screening period: first month
  - Treatment period: 18 months
Dosing

• **Givinostat** oral suspension (10 mg/mL) twice daily in a fed state
• Visits??
• Sites – US site selection is being finalized (Oct/Nov)
Inclusion:
- Age 6-17, DMD confirmed by genetic testing
- Stable dose of steroids for ≥ 6 months
- Climb 4 stairs in ≤ 8 seconds
- Time to rise from floor of <10 seconds at screening
- MRI muscle fat fraction (done in screening)

Exclusion Criteria:
- Have exposure to another investigational drug within 3 months prior to the start of study treatment;
- Have exposure to idebenone within 3 months prior to the start of study treatment;
- Have exposure to any dystrophin restoration product (e.g., Ataluren, Exon skipping) within 6 months prior to study treatment;
- Use of any pharmacologic treatment, other than corticosteroids, with muscle strength effect within 3 months prior to study treatment (e.g., growth hormone); Vitamin D, calcium, and any other supplements will be allowed;
- Have surgery that might have an effect on muscle strength or function within 3 months before study entry or planned surgery at any time during the study;
- Ankle joint contractures of ≥10 degrees; change in treatment <3m or expected during trial
- Have presence of other clinically significant disease, or psychiatric disease
- Have left ventricular ejection fraction <50% at screening;
- Have a current or history of liver disease or impairment;
- Have inadequate kidney function,
- Have a positive test for hepatitis B surface antigen, hepatitis C antibody, or HIV at screening;
BMS-986089
A Monoclonal Antibody designed to block myostatin
Myostatin

• Myostatin
  – Produced primarily in skeletal muscle
  – Is a negative regulator of muscle growth
• In animals genetically engineered to not make any myostatin
  – 2-3 fold increase in body weight
  – Widespread increase in skeletal muscle
  – Decreased fat mass
  – No increase in cardiac muscle
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A Phase 1/2 Study to Evaluate the Safety, Tolerability immunogenicity, PK/PD of BMS-986089

- Age: 5 - <11 years, ambulatory
- N = 40
- 24 weeks of treatment or placebo
- Weekly Sub-cutaneous injection
- After 24 weeks, all roll over into open label 48 week extension
Inclusion/Exclusion

• **Inclusion**
  – DMD 5 – 10 years of age
  – Able to walk without assistance
  – Able to walk up 4 stairs in 8 seconds or less
  – Stable Steroid regimen for > 6 months

• **Exclusion**
  – Use of daytime ventilator
  – Previously currently taking meds like androgens or Human Growth Hormone
Endpoints

• Primary Endpoints:
  – Safety and Tolerability
    • based on number of Adverse Events (AEs) and Serious AEs
    • Based on monitoring vital signs, ECGs, echocardiograms and physical examinations
  – Visit Procedures
    • Vital signs
    • Imaging Studies
    • Timed function Tests, 6 MWT, NSAA
Sites

- UCLA
- Stanford
- DC (CNMC)
- FL (Gainesville, Orlando)
- GA (Atlanta)
- IL (Rush, Chicago)
- KS (Kansas City)
- MD (Kennedy Krieger, Baltimore)
- MO (Wash U, St Louis)
- OH (Cincinnati)
- PA (Pittsburgh)
- CANADA – Alberta, Ontario
PhaseOut DMD
A Phase 2 Clinical Study to Assess Ezutromid (SMT C1100) in Ambulatory Boys with Duchenne
Utrophin Modulation

• Utrophin
  – Functionally and structurally similar to dystrophin
  – Produced during early stage of muscle development and during repair process

• Utrophin modulation
  – Aims to maintain production of utrophin to compensate for lack of dystrophin
Ezutromid Overview

Molecule: First-generation, orally administered utrophin modulator

Status:

> Well-tolerated in ~115 healthy volunteers and 24 boys with DMD
> Received regulatory approval in UK and US to initiate PhaseOut DMD, a Phase 2 proof of concept trial in boys with DMD
> Expect to report data from PhaseOut DMD periodically with 24-week biopsy data from the first group of patients in January 2017
PhaseOut DMD: A Phase 2 Proof of Concept Trial

A 48 week Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with Ezutromid in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy

Overview of key entry criteria:

> 40 male DMD patients
> Age from 5th up to 10th birthday
> Able to walk >300m unassisted in 6 minutes
> Willing to provide two biopsy samples
> Willing to undergo MRI (magnetic resonance imaging)
> On stable steroid regimen for at least 6 months
> 3 month “wash out” after involvement in other clinical trials (excluding those involving ezutromid)
PhaseOut DMD: A Phase 2 Proof of Concept Trial Range of Mechanism and Efficacy Measures

MECHANISM
- Utrophin localization
- Muscle fiber regeneration

MUSCLE HEALTH
- MRI – primary endpoint
- Serum markers

FUNCTION
- Six minute walk distance
- North Star Ambulatory Assessment
Ezutromid Trial

- Open Label (no placebo arm)
- Oral 2x/day, 2500 mg
- Two muscle biopsies – baseline and 24 or 48 weeks
- 12 site visits
  - Screening, weeks 1, 4, 8, 12, 24, 36, 48 plus follow up safety
    - Biomarker measurements and Functional tests
  - Visits to MRI center
    - MRI
Sites

- Children's Hospital of Colorado  Recruiting
- Nemours Children's Clinic  Recruiting
- Boston Children's Hospital  Recruiting
- Cincinnati Children's Hospital Medical Center  Recruiting
- Oregon Health and Science University  Recruiting
- Children's Hospital of Philadelphia  Recruiting
- Vanderbilt University Medical Center  Recruiting
- University of Utah Hospital and Clinics  Recruiting
- Heart of England NHS Foundation Trust - Heartlands Hospital  Enrolling by invitation
- Addenbrooke's Hospital  Active, not recruiting
- Alder Hey Children's NHS Foundation Trust  Enrolling by invitation
- Great Ormond Street Hospital for Children NHS Foundation Trust  Active, not recruiting
- Royal Manchester Children's Hospital  Enrolling by invitation
- The Freeman Hospital, Newcastle Upon Tyne Hospitals  Enrolling by invitation
- UCLA SOON
Duchenne Therapeutic Approaches

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough

- Steroid Replacement
- Anti-Fibrotics
- Inflammation & Fibrosis
- Calcium Regulation
- Ryanodine Receptors
- Calcium Homeostasis

- Dystrophin Restoration/Replacement
- Muscles Growth and Protection
- Treatment Duchenne

- Cardiac
- Blood Flow
- Mitochondria
- Stem Cells
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophin Upregulation

- Traditional Cardiac Drugs
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- Follistatin Upregulation
- Anti-fibrotics
- Anti-sarcolemmal Receptor Modulators
- Anti-Mitochondrial Biogenesis Enhancers

- Coenzyme Q10 and Lisinopril
- CAP-1002
- Gene Transfer of Micro-Dystrophin
- RycalARM210
- AT-300
- Translarna™ (ataluren)
- SRP-4045 and SRP-4053 (ESSENCE)
- RTC13
- NS-065/NCNP-01 for Exon 53 Skipping

- Biogenesis Enhancers
- Stem Cells
Safety and Dose Finding Study of NS-065/NCNP-01 in Boys With Duchenne Muscular Dystrophy (DMD)

- Sponsor: NS Pharma (Nippon Shinyaku Co., Ltd.)
- NS-065/NCNP-01 is an antisense oligonucleotide drug synthesized from morpholino compounds, so that potency and high safety are expected.
- Skips exon 53
Phase 2, multi center, randomized, placebo controlled dose finding

- N= 16
- Ages > 4 < 10
- Confirmed DMD with mutation amenable to exon 53 skip
- Able to walk independently
- Able to complete time to stand, time to run and time to climb assessments
- Stable steroid regimen at least 3 months
- **SITES:** WashU, Davis, Chicago, Emory, UF, Duke, Richmond
Schedule

**Period 1**
- 4 weeks
- 6 patients low dose
- 2 patients placebo

**Period 2**
- Low dose - 20 weeks, High dose - 24 weeks
- 6 patients low dose
- 2 patients placebo
- 2 patients placebo
- 6 patients high dose
- 40mg/kg
- 80mg/kg

**Safety**
- 40mg/kg
- 80mg/kg

**Extension Label**

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE
Resources

• [https://clinicaltrials.gov](https://clinicaltrials.gov)
• DuchenneConnect
• PPMD newsletter
• Companies
• Healthcare Professionals

• Center for Duchenne Muscular Dystrophy at UCLA (Facebook)
THANK YOU TO ALL THE BOYS AND FAMILIES PARTICIPATING IN TRIALS

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